Interview Summary	Application No.	Applicant(s)	
	09/842,547	ADAMS ET AL.	
	Examiner	Art Unit	
	JOHN PAK	1616	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JOHN PAK*. (3)_____.

(2) *JOSEPH SNYDER*. (4)_____.

Date of Interview: *08 December 2004*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *See Continuation Sheet*.

Claim(s) discussed: *All*.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Mr. Snyder authorized an Examiner's Amendment which amends the claims as discussed via the faxes, noted above and attached hereto. In claim 13, the last word in the claim will be changed from "subject" to "animal" in order to correspond to the claim preamble in claim 13*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Exhibit shown or demonstration conducted, If Yes, brief description: On 12/7/2004, Examiner Pak faxed a draft copy of an Examiner's Amendment proposal to Mr. Snyder. Mr. Snyer replied by sending two faxes to the Examiner on 12/8/2004. Copies of the faxes are attached hereto for completeness of the record. The second fax by

Mr. Snyder was in response to the Examiner's request for clarification of "substantial tolerance" claim language.

********** *Urgent* **********

DATE: December 7, 2004

TO: Joseph Snyder

FROM: Examiner John Pak
Art Unit 1616
Tel: (571)272-0620
Fax: (571)273-0620

RE: 09/842,547 (nitroglycerin case)

Mr. Snyder, please review the Ex's Amdt. There are slight differences in language, but I think there is no substantive difference to our original understanding.

This case is after-final and overdue. Please let me know at your earliest convenience. Thanks.

09/842,547
ATTACHEMENT TO INTERVIEW SUMMARY RECORD
PAPER NO. 12072004

Claims 1, 3-5, 13, 16-19, 33-34 are pending in this application. This Office action is in reply to applicant's after-final response of 10/25/2004. Applicant's after-final amendments have been granted entry.

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Snyder on 12/7/2004.

Claim 1. (Currently amended) A method for inhibiting a malignant cell phenotype in a subject, said method comprising: administering to said subject in need thereof a low dose of a nitric oxide mimetic, wherein said nitric oxide mimetic is nitroglycerin, wherein said low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation, and wherein said low dose does not induce the malignant cell phenotype to develop substantial tolerance to said nitric oxide mimetic.

Claim 13. (Currently amended) A method for inhibiting a malignant cell phenotype in an animal, said method comprising: administering to said animal in need thereof a low dose of a nitric oxide mimetic, wherein said nitric oxide mimetic is nitroglycerin, wherein said low dose is 3 to 10,000 fold lower than a dose of said nitric

oxide mimetic that produces vasodilation, and wherein said low dose does not induce the malignant cell phenotype to develop substantial tolerance to said nitric oxide mimetic.

Claim 19. (Currently amended) A method for treating cancer in a subject, said method comprising administering to said subject in need thereof a low dose of a nitric oxide mimetic, wherein said nitric oxide mimetic is nitroglycerin, wherein said low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation, and wherein said low dose does not induce cancer cells in said subject to develop substantial tolerance to said nitric oxide mimetic.

Claim 33. (Currently amended) A method for inhibiting a malignant cell phenotype, said method comprising administering to said malignant cell phenotype a low dose of a nitric oxide mimetic, wherein said nitric oxide mimetic is nitroglycerin, wherein said low dose is delivered by said nitric oxide mimetic at a concentration between about 10^{-14} M to 10^{-6} M, and wherein said low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation.

Claim 34. (Currently amended) The method of claim 33, wherein said low dose is delivered by said nitric oxide mimetic at a concentration between about 10^{-14} M to 10^{-10} M.

09/842,547
ATTACHEMENT TO INTERVIEW SUMMARY RECORD
PAPER NO. 12072004

END of FAX

09/842,547
ATTACHEMENT TO INTERVIEW SUMMARY RECORD
PAPER NO. 12072004

Atty Docket No. 10692V-000520US

PTO FAX NO.: (571) 273-0620

ATTENTION: Examiner John D. Pak Group Art Unit 1614

OFFICIAL COMMUNICATION

FOR THE PERSONAL ATTENTION OF

EXAMINER John D. Pak

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that the following documents in re Application of Michael A. Adams et al., Application No. 09/842,547, filed April 26, 2001 for FORMULATIONS AND METHODS OF USING NITRIC OXIDE MIMETICS AGAINST A MALIGNANT CELL PHENOTYPE are being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Documents Attached

1. Amendments to the Claims

Number of pages being transmitted, including this page: 4

Dated: December 8, 2004

Joseph R. Snyder

PLEASE CONFIRM RECEIPT OF THIS PAPER BY RETURN FACSIMILE AT (415) 576-0300

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, CA 94111-3834
Telephone: 925-472-5000
Fax: 925-472-8895

601373247 v1

Application No. 09/842,547
Ref. No. 10692V-000520US

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:
Listing of Claims:

1. (currently amended) A method for inhibiting a malignant cell phenotype in a subject, said method comprising: administering to **said subject in need thereof** [[cells]] a low dose of a nitric oxide mimetic, wherein said **nitric oxide mimetic is nitroglycerin, wherein said** low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation, and wherein said low dose **of said nitric oxide mimetic** does not induce substantial tolerance **in said subject**.

2. (canceled)

3. (previously presented) The method of claim 1 wherein administration of the nitric oxide mimetic inhibits metastases and development of resistance to antimalignant therapeutic modalities in the cells.

4. (previously presented) The method of claim 1 wherein administration of the nitric oxide mimetic inhibits development of a more aggressive malignant cell phenotype in the cells upon administration of an anti-VEGF agent.

5. (previously presented) The method of claim1 wherein administration of the nitric oxide mimetic inhibits development of a malignant cell phenotype in cells exposed to factors which lower cellular nitric oxide mimetic activity.

6-7. (canceled)

8. (cancelled)

9-12. (canceled)

09/842,547
ATTACHEMENT TO INTERVIEW SUMMARY RECORD
PAPER NO. 12072004

Application No. 09/842,547
Ref. No. 10692V-000520US

13. (currently amended) A method for inhibiting a malignant cell phenotype in an animal, said method comprising: administering to said animal in need thereof a low dose of a nitric oxide mimetic, wherein said **nitric oxide mimetic is nitroglycerin, wherein said** low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation, and wherein said low dose **of said nitric oxide mimetic** does not induce substantial tolerance **in said subject**.

14-15. (canceled)

16. (original) The method of claim 13 wherein administration of the nitric oxide mimetic inhibits tumor metastases and development of resistance to antimalignant therapeutic modalities in cells in the animal.

17. (original) The method of claim 13 wherein administration of the nitric oxide mimetic inhibits development of a more aggressive malignant cell phenotype in cells in the animal upon administration of an anti-VEGF agent to the animal.

18. (original) The method of claim 13 wherein administration of the nitric oxide mimetic inhibits development of a malignant cell phenotype in animals exposed to factors which lower cellular nitric oxide mimetic activity.

19. (currently amended) A method of treating cancer in a subject, said method comprising administering to said subject in need thereof a low dose of a nitric oxide mimetic, wherein said **nitric oxide mimetic is nitroglycerin, wherein said** low dose is 3 to 10,000 fold lower than a dose of said nitric oxide mimetic that produces vasodilation, and wherein said low dose **of said nitric oxide mimetic** does not induce substantial tolerance **in said subject**.

20-21. (canceled)

22. (original) The method of claim 19 wherein the cancer is prostate cancer.

23-29. (canceled)

30-32. (canceled)

Application No. 09/842,547
Ref. No. 10692V-000520US

33. (currently amended) A method for inhibiting a malignant cell phenotype, said method comprising administering to **said malignant cell phenotype** [[cells]] a low dose of a nitric oxide mimetic, wherein said **nitric oxide mimetic is nitroglycerin, wherein said** low dose is **delivered by said nitric oxide mimetic at a concentration** between about 10^{-14} M to about 10^{-6} M ~~of said nitric oxide mimetic~~, and wherein said low dose is 3 to 10,000 fold lower than a dose of **said** [[the]] nitric oxide mimetic that produces vasodilation.

34. (currently amended) The method of claim 33, wherein said low dose is **delivered by said nitric oxide mimetic at a concentration** between about 10^{-14} M to about 10^{-10} M ~~of said nitric oxide mimetic~~.

35.-40 (cancelled)

60372513 v1

09/842,547
ATTACHEMENT TO INTERVIEW SUMMARY RECORD
PAPER NO. 12072004

Atty Docket No. 10692V-000520US

PTO FAX NO.: (571) 273-0620

ATTENTION: Examiner John D. Pak

Group Art Unit 1614

OFFICIAL COMMUNICATION

FOR THE PERSONAL ATTENTION OF

EXAMINER John D. Pak

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that the following documents in re Application of Michael A. Adams et al., Application No. 09/842,547, filed April 26, 2001 for FORMULATIONS AND METHODS OF USING NITRIC OXIDE MIMETICS AGAINST A MALIGNANT CELL PHENOTYPE are being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Documents Attached

1. Communication requested regarding tolerance

Number of pages being transmitted, including this page: 4

Dated: December 8, 2004

Joseph R. Snyder

PLEASE CONFIRM RECEIPT OF THIS PAPER BY RETURN FACSIMILE AT (415) 576-0300

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, CA 94111-3834
Telephone: 925-472-5000
Fax: 925-472-8895

60373247 v1

09/842,547
ATTACHEMENT TO INTERVIEW SUMMARY RECORD
PAPER NO. 12072004

The nitric oxide mimetic of the present invention does not induce substantial tolerance in the subject. As set forth in the specification on page 11, line 15, bridging to page 12:

> Short term nitric oxide mimetic therapy is generally administered at levels which increase nitric oxide mimetic activity of cells above normal physiologic levels. For purposes of the present invention, however, wherein longer term therapy is generally desired, induction of tolerance against the NO mimetic and side effects become concerns. Thus, in the present invention, the amount of nitric oxide mimetic administered is preferably very low so as to delay and/or reduce development of tolerance to the administered NO mimetic and/or unwanted side effects. For example, it is known that administration of nitric oxide or compounds which deliver nitric oxide to human beings at doses conventionally employed to treat cardiovascular conditions (i.e GTN at 0.2 mg/h or greater) by vasodilation can provoke powerful vasodilator responses as well as development of drug tolerance against GTN upon repeated administration. Such administration is often accompanied by a number of undesirable side effects including headache, flushing and hypotension. In contrast, preferred doses of nitric oxide mimetic administered in the present invention to inhibit and prevent a malignant cell phenotype are lower, preferably at least 3 to 10,000-fold lower, more preferably at least 100- to at least 10,000-fold lower than those typically used in other therapeutic applications such as vasodilation and thus do not induce tolerance to the NO mimetic as quickly nor undesirable side effects. [Emphasis added]

As such, the dose of the nitric oxide mimetic administered is low so as to delay and/or reduce development of tolerance [a loss or reduction of the response] to the administered NO mimetic and/or unwanted side effects.

60373767 v1